# IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Koga	mi et	al.		)	Group A	rt 1	Unit:	;
						)	1626			
Appl. No.	:	10/5	23287			)				
						)	Examine	r;		
Filed:	Febru	ary 3	, 200	5		)	Havlin,	Rol	bert	Н
						)				
For :	Proce	ss	for	produ	cing	)				
n-monoalkyl	3-hyd	iroxy-	-3-(2-	thieny	l)pr	)				
opanamine and intermediate						)	•			

# DECLARATION UNDER 37 C.F.R. \$1.132

Commissioner for Patents

PO Box 1450

Alexandria, VA 22313-1450

#### Dear Sir:

- I, \_\_ Kenji Kogami \_ do hereby declare that:
- I am one of the inventors of the above-identified application.
- the experiments given below were carried out under my general direction and supervision.

# Experiment

# 1. Summary and Purpose of Experiment

A (Z)-N-monoalkyl-3-oxo-3-(2-thienyl)propenamine was reduced in the presence and absence of a carboxylic acid. The yields of the resulting N-monoalkyl-3-hydroxy-3-(2-thienyl)propanamine were compared.

### 2. Experimental Methods

### Test 1

0.836 g (0.005 mol) of (Z)-N-monomethyl-3-oxo-3-(2-thienyl)propenamine was dissolved in 4.0 g of toluene, and the resulting solution was heated to 50°C. After adding 0.757 g (0.020 mol) of sodium borohydride to the solution, a reaction was carried out at 80°C for 2 hours. The reaction product was measured by HPLC. The reaction mixture was cooled and washed with an aqueous sodium The solvent was then distilled off under hydroxide solution. ' reduced pressure, and the reaction product was purified using silica gel column chromatography.

## Test 2

A test was conducted in the same manner as in Test 1, except that 0.6 g of acetic acid was added to the solution prior to heating a toluene solution of

(Z)-N-monomethyl-3-oxo-3-(2-thienyl)propenamine to 50°C.

#### Result

The results of HPLC in Tests 1 and 2 are shown in Table 1.

	A (LC area%)	B (LC area%)
Test 1	1.9	91.0
Test 2	77.5	1.5

- \* Sensitivity ratio (mol basis) A:B=1:2.2
- \* A: N-monomethyl-3-hydroxy-3-(2-thienyl)propanamine
  - B: (Z)-N-monomethyl-3-oxo-3-(2-thienyl)propenamine

As a result of silica gel column chromatography, the content of N-monomethyl-3-hydroxy-3-(2-thienyl)propanamine obtained in Test 1 was as low as 0.026 g (yield: 3%), whereas the content of N-monomethyl-3-hydroxy-3-(2-thienyl)propanamine obtained in Test 2 was as high as 0.668 g (yield: 78%).

As is clear from the above, the reduction reaction of (Z)-N-monomethyl-3-oxo-3-(2-thienyl)propenamine hardly proceeds in the absence of acetic acid (Test 1). In contrast, almost all of the (Z)-N-monomethyl-3-oxo-3-(2-thienyl)propenamine was reduced in the presence of acetic acid (Test 2), thereby obtaining an N-monomethyl-3-hydroxy-3-(2-thienyl)propanamine at an extremely high yield.

Analysis

The results reveal that almost no reduction reaction of

(Z)-N-monoalkyl-3-oxo-3-(2-thienyl) propenamine occurs in the

absence of carboxylic acid, whereas almost all of the

(Z)-N-monoalkyl-3-oxo-3-(2-thienyl)propenamine was reduced

in the presence of carboxylic acid, thereby obtaining an

N-monoalky1-3-hydroxy-3-(2-thienyl)propanamine

extremely high yield.

I, the undersigned, declare that all statements made

herein of my own knowledge are true and that all statements

made on information and belief are believed to be true; and

further that these statements were made with the knowledge that

willful false statements and the like so made are punishable

by fine or imprisonment, or both, under section 1001 of Title

18 of the United States Code and that such willful false

statements may jeopardize the validity of the application or

any patent issuing thereon.

Date: June 30, 2009 Kenji Kogami
Kenji Kogami